RSV Infections in Infants: Therapy with a Homeopathic Preparation

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Reprinted from *Biologische Medizin* (1998 April): 71-75.

Abstract

Of a total of 128 infants hospitalized for respiratory syncytial virus (RSV) infections, 66 received Engystol® N intramuscularly for two weeks in addition to standard therapy. The control group of 62 infants received only standard therapy.

By the fifth day of treatment, faster regression of symptoms was noted in the experimental group than in the control group. After two weeks of treatment, a clear increase in phagocytic activity was noted in the experimental group compared to the baseline level.

For two months after discharge from hospital, the infants were administered either oral Engystol® N or placebo. Over the period from two to six months after discharge, the infants in the experimental group contracted significantly fewer respiratory infections than those in the placebo group.

The results of the study indicate that Engystol® N is effective as ancillary treatment of RSV infection in infants, in accelerating symptom resolution during acute infection, and in protecting patients from subsequent respiratory infections.

Resumen

En un grupo de 128 infantes hospitalizados con infecciones RSV (virus sincitial respiratorio), 66 recibieron Engystol® N via inyección intramuscular durante dos semanas además de una terapia convencional. El grupo de control recibió solamente terapia convencional.

Para el quinto día de tratamiento, se observaba una regresión más rápida de síntomas en el grupo experimental que en el grupo de control. Después de dos semanas de tratamiento, un aumento claro fue observado en el grupo experimental comparado al nivel de base.

Durante dos meses después de irse del hospital, los infantes tomaban o Engystol® N oral o placebo. Mientras el período de dos a seis meses después de la salida del hospital, los infantes en el grupo experimental sufrieron muchas menos infecciones respiratorias que el grupo de control.

Los resultados del estudio indican que Engystol® N es efectivo como un tratamiento auxiliar de infecciones RSV en infantes, en la aceleración de resolución de síntomas durante infecciones agudas, y en la protección de los pacientes de infecciones respiratorias subsiguentes.

Introduction

Viral infections are the most frequent cause of respiratory diseases, especially in infants, whose respiratory systems are still immature both structurally and functionally. Their inadequately developed humoral and cellular immunity leads to increased respiratory susceptibility. Thus, viral respiratory infection is the most frequent reason for hospital admissions among infants.[12]

Based upon a worldwide literature search and on this author's own clinical investigation, RSV (respiratory syncytial virus) is the most common and most dangerous pathogen involved in respiratory infections in infants.[15] We found it in 57.6% of 1,287 infants hospitalized for respiratory infections. To date, treatment has consisted of ribavirin therapy, which is used only in high-risk cases because of its adverse side effects.[1, 6, 13] In spite of the problems associated with antibiotic therapy, nearly 50% of hospitalized children are given antibiotics, primarily for the viral/bacterial infections common in this age group. Nosocomial bacterial superinfections are common consequences. In view of these observations, the present study was conducted with the goal of assessing the utility of the homeopathic antihomotoxic agent Engystol® N as an ancillary therapy in infants with RSV infections.

The pilot study was conducted using Engystol® N. This preparation, manufactured by Biologische Heilmittel Heel GmbH, Baden-Baden, Germany, and by Heel Inc., Albuquerque, NM, U.S.A., contains Vincetoxicum 6X, 10X, and 30X in addition to Sulphur 4X and 10X. Since the characteristic effects of antihomotoxic preparations include stimulation and modulation of the immune system and neutralization and elimination of toxins, we saw the potential of this therapy to reduce the use of synthetic pharmaceuticals in pediatrics.

Our primary intention was to answer the question of whether administering Engystol® N in addition to the standard therapy for RSV infections in infants is capable of influencing the following parameters:

- severity of the illness and symptoms
- elimination of RSV antigens from the respiratory tract
- levels of humoral and cellular immunity

Additionally, we hoped to determine:

- whether Engystol® N has any negative effects on the function of vital organs (kidneys, liver) and
- the extent to which it influences the frequency of future viral respiratory infections.

Methods

The study was conducted at the Department of Pediatrics, Warsaw Academy of Medicine (Director: Professor Emilia Torbicka, MD) and at the Virology Laboratory, Warsaw State Institute of Hygiene (Director: Professor Miroslaw Kantoch, MD).

After acceptance by the ethics committee of the Warsaw Academy of Medicine and presentation to the central committee for the registration of clinical studies (in accordance with GCP guidelines), the study was begun in October of 1994. The parents of the infants included in the study were given exact information on the course of the study and gave their consent.

A total of 128 infants took part in the pilot study. The median age at the beginning of the investigation was 5.1 months ± 4.2 months. The presence of RSV was confirmed in all cases on the first or second day of hospitalization.

The infants were randomly divided into two groups and treated either with the standard therapy plus **Engystol® N** (66 cases) or with the standard therapy plus a placebo (62 cases). Each child in the experimental group was given half an ampule or 0.55 ml **Engystol® N** by intramuscular injection daily during the first week of hospitalization and every other day during the second week.

Each child's general condition was evaluated as good, fair, or serious (Figure 1). Regression of symptoms was recorded after 5, 10, and 15 days of treatment using a symptom score on a 5-point rating scale. (Symptom Improvement Score, Figure 2):

1. Disappearance of all symptoms (100%) observed prior to the beginning of treatment

2. Disappearance of 75% of the original symptoms

3. Disappearance of 50% of the original symptoms

4. Disappearance of 25% of the original symptoms

5. No change in the original symptoms

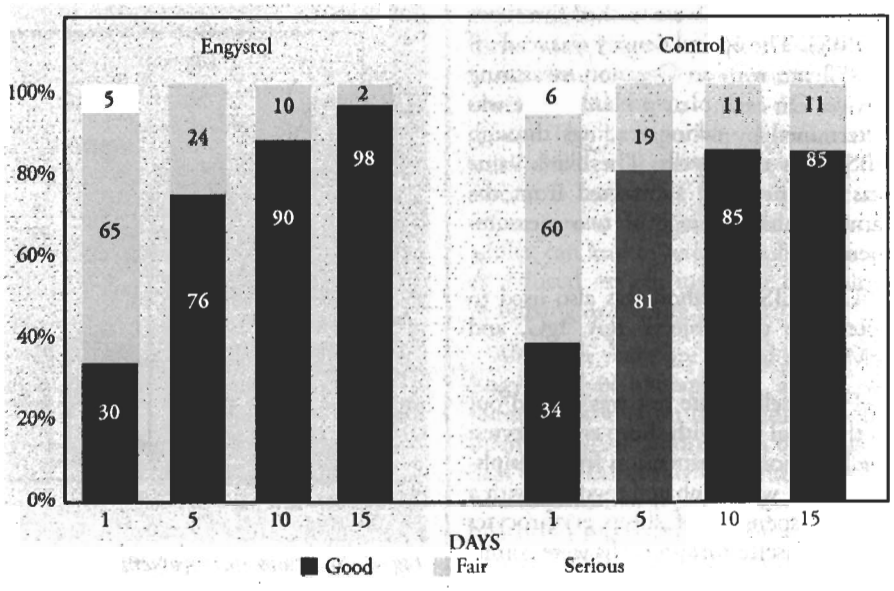

Fig. 1: Degree of severity of clinical symptoms in the Engystol group (standard therapy & Engystol) and control group (standard therapy) during the two weeks of hospitalization.

The following clinical symptoms and parameters were included in the evaluation: fever (rectal temperature over 38.5°C), pharyngitis, rhinitis, cough, dyspnea, auscultatory findings indicating changes in the bronchi, pulmonary parenchyma or bronchioles, X-ray evidence of bronchial or pulmonary infection.

The presence of RSV respiratory infection was confirmed by means of an indirect immunofluorescence assay (IFA) using Wellcome-Serum at the beginning of the study and 15 days after the beginning of treatment. Epithelial cells obtained by swabbing the rear wall of the pharynx were mounted on a slide, dried, and fixed in acetone for 15 minutes. The sample was then covered with antiviral serum and stored for 45 minutes in a moisture chamber at 37° C. After incubation the preparation was rinsed for 30 minutes in distilled water. Once dry, the sample preparations were covered with fluorescein isothiocyanate-conjugated serum. Then the samples were again incubated for 45 minutes at 37°C and rinsed for 30 minutes in distilled water. After drying, the preparations were mounted on slides with buffered glycerin and examined under an ultraviolet microscope (Reichert).

The level of IgG antibodies against RSV was determined by means of ELISA on LINBRO plates. The plates were coated with the antigen (diluted 1:100 in a carbonate buffer with a pH of 9.6) and incubated overnight at 4°C. Then the plates were blocked for two hours at 37°C with 1% bovine albumin (Sigma). After five washings with PBS/Tween 20 (PBST) the plates were stored at 4°C for a period of no more than one week before being examined. Each serum sample was prepared in duplicate (100 µl per well). The result recorded was the difference between the arithmetic mean of the two measurements obtained at OD492 and the blank value (see explanation below).

A 1% albumin solution in PBST (PBSTA) was used to dilute the serums. The microtiter plates were incubated with the serums under investigation for one hour at 37°C. Subsequently, peroxidase-linked anti-human IgG (Cappel) diluted with PBSTA was added and the samples were again incubated for one hour at 37°C. After incubation, the substrate orthophenylenediamine (OPD) in a phosphate-citrate buffer (pH 5.0) and hydrogen peroxide was added. Upon successful staining of the sample the reaction was stopped with 1N sulfuric

acid and the wells were washed five times in PBST. The optical density was read off at 492 nm with an Organon measuring device. On each plate a blank value was determined by taking readings through PBSTA in eight wells. The blank value was obtained and subtracted from the sample value (average of two measurements).

The ELISA method was also used to determine the subjects' IgA, IgG, and IgM titers.

The T-cell rosette test was carried out in the usual way with sheep erythrocytes: the lymphocyte suspension from peripheral blood was incubated together with a 0.5% suspension of sheep erythrocytes and the rosette-forming cells were counted under the microscope at a magnification of 400x. Cells with at least three attached erythrocytes were counted as rosettes.

The nitroblue tetrazolium test (to determine intracellular phagocyte metabolism) is based on the fact that nitroblue tetrazolium (NBT) turns yellow in solution. In phagolysosomes it is reduced to insoluble, dark blue formazan. A suspension of granulocytes from peripheral blood was incubated together with the NBT reagent and a suspension of latex particles. A smear was taken of the cell sediment and stained using the Pappenheim method. Evaluation was conducted at a magnification of 1000x and the results expressed as the percentage of phagocytic cells (cells containing formazan granules).

The two weeks of intramuscular **Engystol®** N therapy for RSV infections was continued in a double-blind test against a placebo. The group of subjects treated with **Engystol®** N in the hospital continued the treatment in tablet form and were given either **Engystol® N** or the placebo twice daily. The double-blind was decoded upon conclusion of the study.

The first monitoring examination took place two months after discharge from the hospital and immediately following the conclusion of the two months of administering **Engystol® N**. The second monitoring examination took place four months after the conclusion of **Engystol® N** therapy (six months after discharge from hospital). The results were subjected to statistical analysis using the Kruskal-Wallis, Wilcoxon, Fisher's exact, and Kendall's tau-b tests, with the level of significance assumed to be $p = 0.05$.

This part of the study recorded primarily post-hospitalization frequency of respiratory infections.

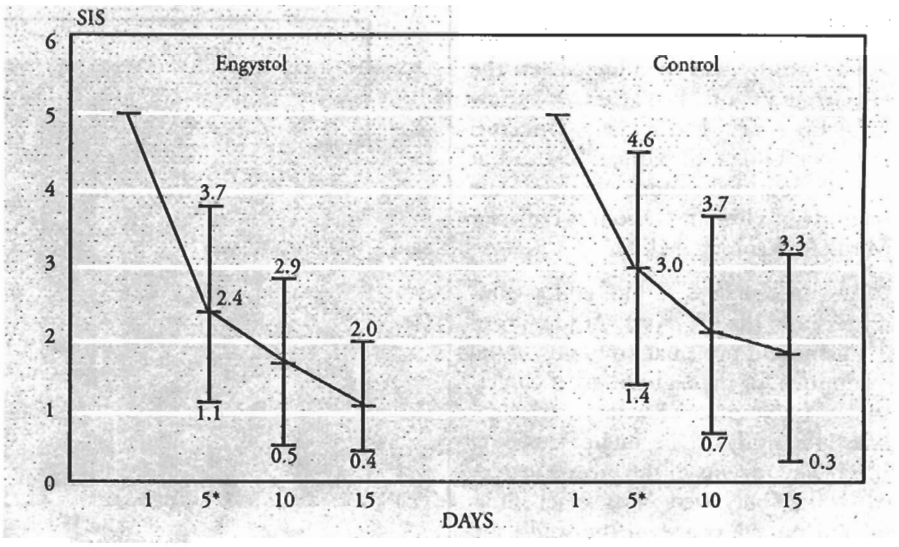

*Fig. 2: Symptom improvement in the Engystol group (standard therapy & Engystol) and control group (standard therapy.) SIS = symptom improvement score; 5.0 = all initial symptoms present; 1.0 = all initial symptoms gone; *p = 0.03 (Kruskal-Wallis)*

Results

At the time of their initial examination in the hospital, 65% of the infants suffering from RSV infections (n = 128) were in "fair" condition, while only 5% were in "serious" condition, which was surprising because 88% of the children were suffering from lower respiratory infections (pneumonia and/or bronchiolitis).

Although no significant differences were found between the severity of the general conditions of the two groups (**Engystol® N** group and control group) during the evaluations on days 5, 10, and 15 of their hospitalization, almost 100% of the children who received supplemental treatment with **Engystol® N** were already in good general condition on day 15, while the same improvement had occurred in 89% of the control group.

By day 5 of treatment with **Engystol® N** it was apparent that the average score for symptomatic improvement (Symptom Improvement Score = SIS) was considerably lower in the **Engystol® N** group than in the control group (2.4 ± 1.3 versus 3.0 ± 1.6). On days 10 and 15 the SIS of the **Engystol® N** group was also less than that of the control group, although not substantially so ($p = 0.058$, Figure 2).

The greatest difference between the groups was seen in the NBT test (Figure 3). At the time of the first examination the average NBT values of the two groups were not significantly different: 6.5 ± 5.8% in the **Engystol® N** group and 7.9 ± 6.6% in the control group. However, it should be noted that in the **Engystol® N** group the NBT value was below the normal range (11 ± 4.0%), while in the control group it fell within the normal range. After two weeks of treatment, average test values for the two groups differed significantly ($p = 0.008$). In the experimental group, the average NBT value rose after treatment from 6.5 ± 5.8% to 11.6 ± 8.5% ($p = 0.002$), thus entering the normal range. It was also significantly higher ($p = 0.008$) than the average value in the control group, which sank below the normal range to 6.5 ± 4.6%.

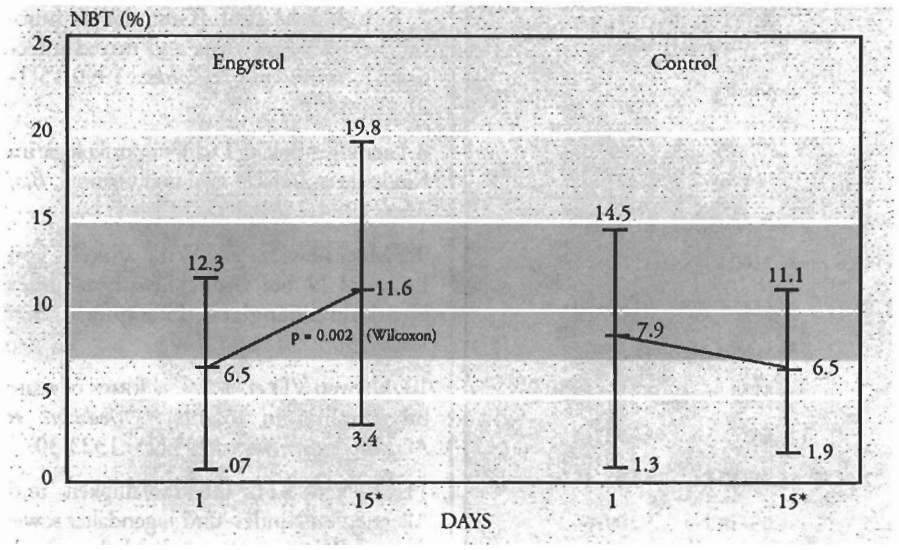

*Fig. 3: NBT Test (phagocytic activity) at the start and at day 15 for the Engystol group (standard therapy & Engystol) and control group (standard therapy.) *p = 0.008 (Kruskal-Wallis)*

The Table summarizes the results of the other tests that were conducted upon admission to the hospital and again two weeks later (day 15 of observation). No significant differences between the two groups were determined in the average values of the tested parameters, and no differences at the chosen level of significance were found between the two groups before and after treatment. **Engystol®** N therapy did not increase elimination of the RSV antigen. Similarly, there were no significant differences in the titers of specific antibodies (IgG, IgA, IgM) to RSV or in the T-lymphocyte erythrocyte rosette test (TE rosette test) and erythrocyte sedimentation rate (ESR).

Since no significant changes in serum transaminase and creatinine levels were found after treatment, it appears that **Engystol®** N has no adverse side effects on liver and kidney functions.

After two months only 28 children from the **Engystol®** N group and 14 from the placebo group appeared for the follow-up examination. With respect to the number of incidents of infection no significant differences between the two groups were determined. Sixteen children (57%) from the **Engystol®** N group and seven (50%) from the control group had contracted infections in the interim. Respiratory infections were not significantly more frequent in the control group, occurring in 19 out of 28 children in the **Engystol®** N group and 12 out of 14 in the control group. Children in the placebo group were more likely to have had more than one infection.

Although only 20 children from the **Engystol®** N group and 11 from the control group were available for follow-up examination six months after hospitalization, it was possible to determine statistically significant differences between the groups. During that period of time, 9 children (45%) from the **Engystol®** N group and 10 (91%) from the control group had contracted an infection ($p < 0.0025$ Fisher's exact and $p = 0.0011$ tau-b). In the **Engystol®** N group, infections were also several times less frequent than in the control group (9 episodes in 20 children versus 18 episodes in 11 children [Wilcoxon $p < 0.012$, Kruskal-Wallis $p < 0.0011$]). Half of the children who received the placebo had experienced several episodes.

Discussion

This study indicates that supplementing standard treatment of pediatric RSV infections with the homeopathic antihomotoxic agent **Engystol®** N has a positive effect.

Already after the first monitoring examination on the fifth day of treatment with **Engystol®** N, considerably faster symptomatic improvement was observed in comparison to the control group. This is especially significant in small children because the course of the disease is less severe. For example, in infants, even rhinitis, a mild illness in adults, can lead to serious problems such as reduced oxygen intake or difficulties in nursing or feeding.

Although there are several studies of **Engystol®** N therapy for adults, we found no studies on this medication for infants or small children. On the basis of data in the literature on homotoxicology, we expected that the homeopathic combination preparation **Engystol®** N (whose effects purportedly include helping to regulate the exchange of water, electrolytes, and oxygen in connective tissue) would be helpful in maintaining homeostasis in the infantile organism.

The cases investigated in this study suggest that by neutralizing and eliminating toxins formed during infection and by enhancing the body's natural resistance, resulting in faster recovery, **Engystol®** N might play an important part.[3, 5, 8, 11, 14] Immunoregulatory effects are especially important in viral infections because viruses weaken the child's immune system; among other things, phagocyte activity (important in fighting infections) is reduced.[3, 7] The present study confirmed this virus-induced reduction in phagocyte activity: two weeks after the beginning of the infection NBT values (confirmation of the bactericidal activity of phagocytes) fell below normal levels in the control group. Various factors are known to cause this disorder in phagocytosis. In contrast, in the group treated with **Engystol®** N, average NBT values rose significantly between day 1 and day 15.

Engystol® N appears to exert a stimulatory effect and improve the bactericidal capability of phagocytes. In the first phase of the viral infection, phagocytic capability was below the normal range (in the NBT test).

Wagner *et al.* have reported improvement in phagocytosis in adults as a result of **Engystol®** N.[14]

Test	Engystol Group		Control Group	
	Beginning	Day 15	Beginning	Day 15
RSV-Antigen [%]	100	46.97	100	41.94
RSV-Antibodies [OD_{492}]	0.09±0.09	0.11±0.19	0.10±0.16	0.11±0.16
IgA [mg/dl]	36.3±35.8	49.2±60.0	35.2±43.3	37.2±27.5
IgM [mg/dl]	125.9±144.1	136.4±149.6	95.2±60.8	117.0±98.7
IgG [mg/dl]	471.6±264.3	477.2±248.1	498.4±241.6	515.2±201.9
TE-Rosettentest [%]	30.9±11.3	29.4±12.4	38.5±49.4	27.8±15.7
ESR [mm/h]	21.0±20.4	12.2±9.5	21.6±23.0	11.3±11.6
positive X-ray findings [n,%]	27.41	12.30	29.46	21.53
AspAT [I.E./l]	50.59±19.94	51.47±22.54	55.31±32.64	58.07±36.04
AlAT [I.E./l.]	35.96±13.96	39.72±25.6	46.06±48.2	54.09±60.3
Creatinine [mg/dl]	0.32±0.12	0.35±0.09	0.35±0.1	0.34±0.1

Tab.: Results of various tests. ESR = erythocyte sedimentation rate; AT = aminotransferase (transaminase).

Our observation may have important practical value. If **Engystol® N** increases the bactericidal activity of phagocytes, this preparation could have a positive effect on bacterial superinfections and may possibly reduce the use of antibiotics. The problem of how to implement alternative methods in order to reduce antibiotic use is being tackled on the international level. Antihomotoxic medicine might have an important part to play in these trials.

The present pilot study encompassed only a relatively small number of patients, especially in the follow-up phase. However, since it showed that during the double-blind comparison (two to six months after discharge from hospital), significantly fewer children in the group that had previously been treated with **Engystol® N** contracted respiratory infections than those in the placebo group, it appears that **Engystol® N** has a prophylactic effect against RSV respiratory infections in infants. Heilmann showed that adults treated with **Engystol® N** had less severe symptoms and a lower rate of upper respiratory infections.[4]

The results we obtained should now be confirmed using a larger number of infants and a longer follow-up period. In addition, the optimum dosage and duration of therapy in treating small children should also be determined.

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